Case Reports

Pseudofractures in Patients With Low-Turnover Osteoporosis

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PSEUDOFRACTURES (Looser's zones, Milkman's fractures) were first described in Germany and Austria in the period immediately following World War I.[1-3] Their cause was considered to be lack of adequate nutrition (hunger osteopathy) and many of the cases initially reported to have this radiographic finding had evidence of osteomalacia or rickets. In 1930 Milkman described the first case of pseudofractures in the English literature.[4] They are characteristically linear, radiolucent areas, frequently with sclerotic margins, that most commonly occur perpendicular to the periosteal surface in ribs, scapulae, the pelvis and long bones. Their presence has proved to be a useful roentgenographic sign of osteomalacia. In fact, recent reviews of osteomalacia have emphasized the diagnostic value of pseudofractures and have reasserted that pseudofractures are a pathognomonic sign of that disorder.[5,6] We report, however, two patients in whom multiple, symmetric pseudofractures occurred in the presence of low-turnover osteoporosis and in the absence of any evidence of osteomalacia.

Reports of Cases

Case 1

The patient, a 73-year-old woman, was referred to the Bone and Mineral Clinic at The Oregon Health Sciences University for evaluation of osteopenia presumed to be due to osteomalacia. A year earlier she had the onset of sharp or aching bilateral inguinal pain that was considerably worsened with weight bearing or hip movement. After several months of gradually increasing discomfort, she sought treatment from a chiropractor who "manipulated" her pelvis. These manipulations were carried out periodically over a six-month period but the discomfort continued and she was finally confined to a wheelchair. She saw a physician and a radiograph showed pseudofractures in all four pelvic rami (Figure 1). A technetium Tc 99m diphosphonate bone scan showed increased uptake in those areas but was otherwise unremarkable.

The patient said she had had no previous bone disease, rickets, bone tenderness, back pain, diarrhea, weight loss, operations, alcohol use or renal disease. The patient's only medications were six tablespoons per day of Maalox or Mylanta for esophageal reflux (two years) and one multivitamin per day that contained 400 IU of ergocalciferol (two months). She had received a two-month course of estrogen therapy that had been discontinued five years before.

On physical examination she was mildly obese and had mild dorsal kyphosis without vertebral tenderness or scoliosis. There was minimal tibial and clavicular tenderness and slight generalized weakness. An initial laboratory evaluation elicited the following values: serum creatinine, 1.0, calcium, 9.6, and phosphorus, 3.5 mg per dl; total protein, 7.4 grams per dl; alkaline phosphatase, 118 mU per ml (normal, 35 to 105). Serum aspartate aminotransferase (AST, formerly glutamic-oxaloacetic transaminase) and bilirubin concentrations were normal. Serum 25-hydroxycholecalciferol level was 36 ng per ml (normal, 10 to 50) and serum 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D_3) concentration was 53 pg per ml (normal 30 to 75). Fasting urinary adenosine 3′:5′-cyclic phosphate concentration was 3.4 nmol per dl glomerular filtration rate (normal, 1.8 to 4.5) and 24-hour urine calcium excretion was 114 mg while on a routine diet.

Radiographs of the lumbosacral spine showed osteopenia with anterior wedge fractures of L-2 and L-3. Single-photon absorptiometry done at the junction of the distal and middle thirds of the radius showed a bone mineral content of 0.64 grams, bone width of 1.2 cm and bone mineral content/bone width of 0.53 grams per cm^2 (normal for age and sex, 0.57 ± 0.085 standard deviation [SD]). At the distal radial site (2 cm proximal to the ulnar styloid), the bone mineral content was 0.7 grams, bone width 2.5 cm and bone mineral content/bone width 0.28 grams per cm^2 (normal, 0.4 ± 0.103 [SD]).

A percutaneous trephine bone biopsy was done and an 8-mm specimen obtained from the iliac crest after tetracycline labeling; it was processed by nondecalcifying methods,[7] sectioned and stained for histomorphometric analysis (Robert Recker, MD, Creighton University, Omaha, Neb) (Table 1). The trabecular bone volume was greatly depressed (6%) and both static and dynamic measures of bone remodeling were

TABLE 1.—*Histomorphometric Features of Two Cases of Pseudofracture*

	Case 1	Case 2	Normal	
Trabecular bone volume, cu mm	0.066	0.043	0.148	±0.033*
Osteoid volume, mm	....	....	0.0034	±0.0024*
Osteoid seam width, cu mm	0.0059	0.0065	0.00639	±0.00072*
Fractional osteoid surface, %	0.115	0.14	0.121	±0.075*
Fractional double-labeled surface, %	0.0066	....	0.123	±0.015*
Fractional resorption surface, %	0.0297	0.0617	0.039	±0.009*
Mineralization lag time, yr (range)	0.618	....	0.0575 (0.023-0.143)	
Bone formation rate, cu mm/yr	0.0095	....	0.381	±0.152*

*Mean ± standard deviation.

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ABBREVIATIONS USED IN TEXT
AST = aspartate aminotransferase
SD = standard deviation

decreased with an osteoid seam width of less than 6 microns, a fractional resorption surface of less than 3% and fractional double-labeled surface of less than 1%. The osteoid volume was uncalculable (none of the grid reticule points fell on osteoid). However, there was a notable amount of trabecular surface covered with very thin osteoid seams such that the fractional osteoid surface measurement was at the mean for normal. The mineralization lag time was depressed at 0.618 years and the bone formation rate was severely depressed.

A pelvic radiograph done eight months after that shown in Figure 1 and before any therapy was begun showed no further evidence of healing. Therapy with a combination of sodium fluoride, vitamin D and calcium was begun but, despite therapeutic serum concentrations of fluoride, there had been no further improvement in the radiographic appearance of the pelvic fractures after ten months of therapy.

Case 2

The patient, a 75-year-old woman, was referred to the Bone and Mineral Clinic at The Oregon Health Sciences University for evaluation of bone disease. She had been well until 12 years earlier when she began to experience back discomfort. Five years before the current evaluation, the diagnosis of Paget's disease or osteomalacia, or both, had been made on the basis of bilateral femoral diaphyseal pseudofractures and an elevated serum alkaline phosphatase level. A regimen of porcine calcitonin, 100 IU given subcutaneously three times per week, was begun for presumed Paget's disease, and 50,000 units of ergocalciferol with 1,500 mg of calcium carbonate per day was administered for presumed osteomalacia. She subsequently sustained several vertebral crush fractures, a right femoral shaft fracture through the pseudofracture and, finally, six months before evaluation, a left femoral shaft fracture at a site distinct from the pseudofracture. All fractures were associated with minimal trauma.

She had undergone a natural menopause 20 years previously and was started on a regimen of diethylstilbestrol at age 72. Vaginal bleeding prompted a hysterectomy eight months later but she continued the diethylstilbestrol therapy. A benign thyroid nodule had been removed at age 68 and the patient received 3 grains of desiccated thyroid daily thereafter. A mastectomy had been done 15 years earlier for a malignant lesion but there was no evidence of recurrent disease. There was no history of other systemic disease, operations or of other medications known to affect bone metabolism.

On physical examination her weight appeared normal, she had only slight kyphosis and was without bone tenderness. Laboratory studies elicited the following values: serum creatinine, 0.7, calcium, 10.7 (normal, 8.5 to 10.5), and phosphorus, 4 mg per dl; total protein, 7.4 grams per dl, and alkaline phosphatase, 181 mU per ml (normal, 35 to 105). Serum AST and bilirubin concentrations were normal. The serum free thyroxine concentration was 1.1 ng per dl (normal, 0.7 to 1.8). A 24-hour urine calcium excretion was 148 mg while on a routine diet. The serum 25-hydroxycholecalciferol level was 152 ng per ml.

A radiographic evaluation showed generalized osteopenia, multiple wedge and compression fractures of the thoracic and lumbar spine and a pseudofracture of the medial aspect of the proximal left femoral shaft (Figure 2, left and middle). Orthopedic plates were present at the site of repair of the previous right femoral fracture, but a linear lucent zone at the site of the fracture had not yet healed (Figure 2, right). Reviews of previous femoral radiographs showed that a pseudofracture very similar to the one apparent in the left femoral shaft had been present at the site of the right femoral fracture.

Radial-photon absorptiometry done at the junction of the distal and middle thirds of the radius showed a bone mineral content of 0.48 grams, a bone width of 1.08 cm and a bone mineral content/bone width of 0.44 grams per cm^2 (normal, $0.57 \pm .085$ [SD]). At the distal radial site (2 cm proximal to the tip of the ulnar styloid) the bone mineral content was 0.51 grams, bone width was 2.28 cm and bone mineral content/bone width was 0.22 grams per cm^2 (normal, 0.4 ± 0.103 [SD]).

Histologic review of bone material obtained at the time the right femoral fracture was reduced five years earlier showed no evidence of Paget's disease, and a further review of radiographic examinations showed no lesions characteristic of Paget's disease. Histologic sections of bone from the reduction of the left femoral fracture were not available. A percutaneous trephine bone biopsy was done and an 8-mm specimen obtained from the left iliac crest was processed by nondecalcifying methods,[7] sectioned and stained for histomorphometric

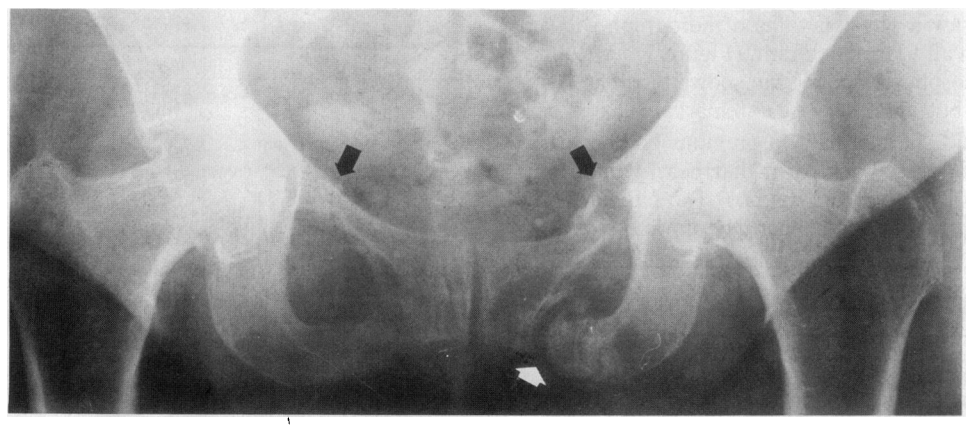

Figure 1.—Pelvic radiograph of patient 1 showing pseudofractures (arrows) of pelvic rami.

analysis (Robert Recker, MD). That analysis (Table 1) showed greatly depressed trabecular bone volume (5%). Static measures of bone remodeling showed a fractional osteoid surface of 14% and a fractional resorption surface of 6%. Because the trabecular bone volume was very low and there was very little osteoid present, no grid points fell on osteoid and thus the osteoid volume was not derived. There was very little trabecular bone surface on which formation rates could take place and there were no double labels present on trabecular surfaces (fractional double-label surface, mineralization lag time and bone formation rate were therefore not calculated). Nevertheless, trabecular remodeling was apparently depressed. Several areas of double tetracycline labeling appeared on cortical endosteal surfaces, indicating that the patient had taken and absorbed the tetracycline.

The ergocalciferol therapy was discontinued and the serum calcium level subsequently became normal. Other drug therapy was continued and sodium fluoride was added to the regimen. After eight months the patient had sustained several more thoracic vertebral crush fractures but was tolerating the sodium fluoride well. A repeat radiographic examination of the femurs showed no futher evidence of fracture healing.

Discussion

In 1930 Milkman[4] described a case of a patient with nephritis and a generalized skeletal disorder characterized radiographically by osteopenia and multiple, symmetric, ribbonlike zones of decalcification or "pseudofractures." He later termed the condition "multiple spontaneous idiopathic symmetrical fractures" and suggested it represented a new skeletal disease of unknown cause.[8] The actual clinical implications of the presence of pseudofractures evoked considerable controversy[9,10] until 1946 when Albright and co-workers[11] argued convincingly that pseudofractures in fact represent a manifestation of osteomalacia of any cause. They cited work by Looser who had extensively studied the phenomenon of pseudofractures and concluded that mechanical irritation and local microfracture resulted in callous formation within bone.[12,13] The mineralization defect of osteomalacia prevents this "zone of transformation" (umbauzonen) from mineralizing and a radiolucent area (pseudofracture) results. In fact, the histologic appearance of pseudofracture in osteomalacia is indeed that of unmineralized callus.[12] Whereas radiolucent defects similar to pseudofractures may occur in cases of Paget's disease or osteogenesis imperfecta, the other radiographic manifestations of those disorders are always present as well.[11] Stress fractures, another cause of radiolucent zones similar in appearance to pseudofractures, are a result of mechanical stress and heal rapidly following relief of that stress. Albright and associates concluded, therefore, that "ribbon-like zones of decalcification, which occur in otherwise normal-appearing bone, which last months or years without regressing, and which exhibit a marked tendency to be symmetrical, occur only in osteomalacia or rickets."[11] The perception that pseudofractures are a pathognomonic feature of osteomalacia persists in recent reviews.[5,6]

In contrast, the patients in the two cases reported here manifested radiographic lesions indistinguishable from pseudofractures in their appearance and symmetry. Although the inciting events resulting in the appearance of the fractures are unknown (acute or prolonged mechanical stress, perhaps related to the chiropractic manipulation in case 1), their duration is inconsistent with simple traumatic fracture or stress fracture. Whereas the lesions were not in themselves histologically evaluated, histomorphometric analysis of iliac crest bone biopsy specimens in each case showed osteoporosis with greatly depressed indices of bone remodeling. In both cases the presence of pseudofractures resulted in the initial diagnosis of osteomalacia. In case 2 the therapy for presumed

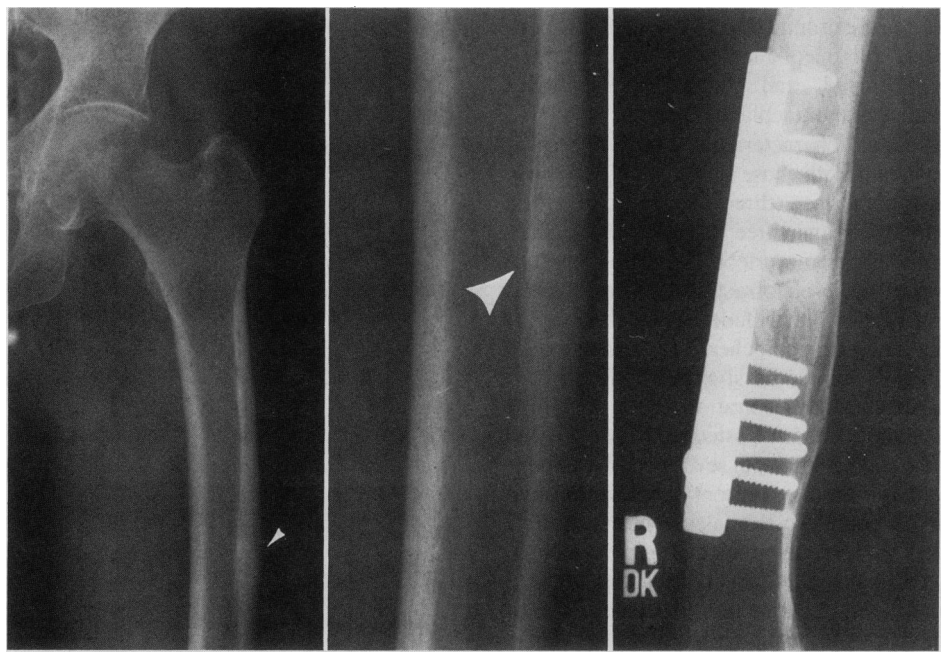

Figure 2.—Left, Radiograph of proximal left femur of patient in case 2 showing femoral pseudofracture (arrow). **Middle,** Close-up of left femoral pseudofracture (arrow). **Right,** Right femoral radiograph showing zone of lucency at the site of a previous fracture.

TABLE 2.—*Clinical Characteristics of Six Women With Pseudofractures in the Absence of Osteomalacia*

Case	Age	Fracture Location	Serum Calcium	Serum Phosphorus	Alkaline Phosphatase	Bone Histomorphometry	Source
1	73	Pelvis	N	N	Elevated	Low-turnover osteoporosis	This study
2	75	Femur	N	N	Elevated	Low-turnover osteoporosis	This study
3	40	Multiple	N	N	N	. . .	Richardson et al, 1978[14]
4	34	Multiple	N	N	N	. . .	Richardson et al, 1978[14]
5	64	Femur	N	N	N	. . .	Perry et al, 1982[15]
6	33	Femur	N	N	N	. . .	Perry et al, 1982[15]

*N = normal

osteomalacia of ergocalciferol and calcium was associated with supranormal concentrations of 25-hydroxycholecalciferol and hypercalcemia, which resolved with discontinuance of the ergocalciferol. The pathophysiology of the osteopenia in these two patients is unknown but several potential risk factors were present in each patient—case 1: age, postmenopausal state and aluminum-containing antacid use; case 2: age, postmenopausal state, desiccated thyroid therapy, ergocalciferol therapy. In case 2 calcitonin therapy probably did not contribute to a progression of osteopenia.

Several other patients have had pseudofractures occurring in the absence of osteomalacia. Richardson and colleagues[14] reported the cases of two premenopausal women who presented with skeletal pain of five to ten years' duration, multiple pseudofractures (nonsymmetric) and no biochemical or histologic evidence of osteomalacia. Treatment with a regimen of calcium and vitamin D resulted in no improvement. Similarly, Perry and associates[15] described the cases of two women (one premenopausal and one postmenopausal) who presented with bilateral, painful femoral pseudofractures of nine months' and eight years' duration. Once again there was no biochemical or histologic evidence of osteomalacia. In one patient, treatment with calcium and vitamin D for presumed osteomalacia resulted in the prompt development of hypercalcemia. A traumatic completion of a femoral neck pseudofracture subsequently occurred, and nonhealing eventually resulted in the need for a total hip replacement.

In Table 2 the clinical characteristics of the two cases described here are shown with those of the four previously reported cases. All were women (three were premenopausal and three postmenopausal) and three had other roentgenographic evidence of osteopenia (vertebral compression fractures). The location of the pseudofractures was most commonly femoral (five of six) but included a wide variety of sites. In four women, all routine biochemical variables were normal, whereas in two there were slight elevations in the serum alkaline phosphatase concentration. Bone histology was characterized by the absence of osteomalacia in all, and pronounced trabecular osteopenia with severely reduced bone remodeling was found in the two present cases. In two patients the treatment of presumed osteomalacia with vitamin D and calcium resulted in the development of hypercalcemia, which was quickly corrected with the withdrawal of therapy. Finally, the potential seriousness of the syndrome is underscored by the occurrence of completed femoral fractures in two patients.

These cases show that multiple pseudofractures characterized by symmetry and delayed resolution are not always the result of an osteomalacic process, and that the metabolic bone disease underlying the development of pseudofractures may include osteoporosis. Potentially more appropriate therapy for osteoporosis was considerably delayed in these patients by the erroneous diagnosis and therapy for osteomalacia. Furthermore, the occurrence of hypercalcemia in two patients with this syndrome (during treatment with vitamin D and calcium) illustrates the risks of treating for presumed osteomalacia without histologic verification. These cases indicate the diagnostic value of the percutaneous bone biopsy and bone histomorphometry, particularly in the absence of the biochemical concomitants of osteomalacia (hypocalcemia, hypophosphatemia and elevated alkaline phosphatase concentration).

The pathophysiology of pseudofractures in the absence of osteomalacia is unknown but may involve defects in new bone formation and a resultant inadequacy of repair at sites of stress or microfracture (the Looser hypothesis). In the two cases reported here, the pronounced depression in bone remodeling and specifically in the rate of new bone formation may have prevented an appropriate healing response, resulting in the development of pseudofractures.

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